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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/572,811
Filing Date: March 22, 2006
Appellant(s): EDENS ET AL.

Leonard C. Mitchard
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 04/01/2011 appealing from the Office action mailed 09/01/2010.

(1) Real Party in Interest

The examiner has no comment on the statement, or lack of statement, identifying by name the real party in interest in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The following is a list of claims that are rejected and pending in the application:

Claims 9, 11, 12 and 23-31 (as amended on 01/03/2011) are pending in this application, and have been finally rejected.

(4) Status of Amendments After Final

The examiner has no comment on the appellant's statement of the status of amendments after final rejection contained in the brief.

(6) Grounds of Rejection to be Reviewed on Appeal

The examiner has no comment on the appellant's statement of the grounds of rejection to be reviewed on appeal. Every ground of rejection set forth in the Office action from which the appeal is taken (as modified by any advisory actions) is being maintained by the examiner except for the grounds of rejection (if any) listed under the subheading "WITHDRAWN REJECTIONS." New grounds of rejection (if any) are provided under the subheading "NEW GROUNDS OF REJECTION."

(7) Claims Appendix

It is noted that in the advisory action sent by the office on 01/20/2011, claims 25 and 26 were objected to as they depended from a canceled claim 10, which have been amended by appellants to correct the dependency of said claims in the claims appendix submitted with the brief.

The examiner has no additional comment on the copy of the appealed claims contained in the Appendix to the appellant's brief.

(8) Evidence Relied Upon

WO 02/45524 A2 DEKKER ET AL 13 June 2002.

MESSER, M. et al. "ORAL PAPAIN IN GLUTEN TOLERANCE", Lancet, vol. 2 (7993), (Nov 6, 1976), pp. 1022.

HAUSCH, F. et al. "INTESTINAL DIGESTIVE RESISTANCE OF IMMUNODOMINANT GLIADIN PEPTIDES", Am. J. Physiol. Gastrointest. Liver Physiol., volume 283, (Oct 2002), pp. G996-G1003 (First published on June 5th, 2002).

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 9, 11, 12 and 23-31 (as amended on 01/03/2011) are/remain rejected under 35 U.S.C. 103(a) as being unpatentable over Messer et al (1976) in view of Hausch et al (2002) and Dekker et al (WO 02/45524 A2).

Claims have been interpreted as generally directed to a method of treatment of patients in need thereof or patients suffering from celiac disease (elected specie of disease), wherein the

method requires oral administration (i.e. *via* ingestion route) of a dietary supplement or a medicament (taken as a pharmaceutical composition) comprising a proline specific endoprotease (PEP; obtained from *Aspergillus niger*; that can hydrolyze proline-rich peptides that are associated with the occurrence of celiac disease at a pH of below 5.5, or that has a pH optimum below 6.5; and which is active in the stomach of the patient, and is pepsin resistant; see specific recitations of claims 9 and 11, as amended).

Messer et al (1976) disclose a method of treatment of patients in need thereof (or patients suffering from celiac disease), wherein the patients are orally administered a dietary formulation or supplement comprising a digestive enzyme (i.e. oral enzyme therapy to treat celiac disease; see entire report at page 1022, entire article) such as papain (in the form of enteric-coated tablets of commercially available crude papain enzyme) in order to help destroy the gluten to improve response to gluten free diet in the patients suffering from celiac disease, wherein based on their positive and encouraging experimental results, they recommend oral, crude papain enzyme administration as an adjunct treatment to the gluten-free diet in the treatment of gluten intolerance in patients in need thereof.

Briefly, Messer et al disclose oral enzyme therapy for patients with celiac disease using administration of crude papain preparations (albeit, in the form of enteric-coated tablets in order to prevent inactivation of papain in the acidic pH of the patient's stomach).

However, Messer et al do not explicitly disclose the use of **proline specific endoprotease** (PEP) that **is pepsin resistant**, and has the hydrolytic activity at **pH below 5.5, or a pH optimum of below 6.5**, as required by the instant claims.

Hausch et al (2002) disclose the immunodominant gliadin peptides that are now known to be the cause of celiac disease or gluten intolerance, and they also show that these peptides are exceptionally resistant to enzymatic digestion in patients with such disorders as celiac disease (see abstract, and introduction, in particular). They also disclose the fact, that trace amounts of exogenously added (both, *in vitro* or *ex vivo*) prolyl endopeptidase (albeit from a bacterial source) was able to efficiently destroy or digest said immunodominant peptides, suggesting "*a possible enzyme therapy strategy for celiac sprue...*" (see abstract, page G996, in particular). Hausch et al also contemplate that "*...therefore, we suggest that supplementation of the celiac diet with bioavailable PEP, with or without DPP IV and DCP I, by virtue of facilitating gliadin peptide cleavage to nontoxic and/or digestible fragments may be useful in attenuating or perhaps even eliminating the inflammatory response to gluten. Such a strategy would be analogous to the* ***enzyme therapy treatment*** *in the case of lactose intolerance,* ***where orally administered lactase is effective in cleaving and thereby detoxifying the lactose in milk product***" (see page G1002, left column, and references contained therein).

In brief, Hausch et al disclose the benefits of using proline specific endopeptidase (albeit, obtained from a bacterial source) that can be employed as an oral enzyme therapy in order to effectively destroy or digest the immunodominant gliadin peptides that are known to cause celiac sprue in susceptible patients.

Therefore, given the disclosure by the cited prior art references of record, at the time this invention was made, it would have been obvious to a person of ordinary skill in the clinical art to modify the method of treatment disclosed by Messer et al such that it uses a dietary supplement comprising prolyl endopeptidase as explicitly suggested by the disclosure of Hausch et al. Since,

Hausch et al clearly demonstrated the use of prolyl endopeptidase in destroying the immunogenic gluten peptides that are known to be the root cause of the inflammatory response in patients with celiac disease, an artisan of ordinary skill in the clinical art would be motivated to substitute the enzyme, papain (used by Messer et al) with the prolyl endopeptidase of Hausch et al in order to successfully destroy hard to digest gliadin peptides, and thus achieve a superior and effective method of treatment of patients in need thereof, or patients having celiac disease.

However, the cited references of Messer et al and Hausch et al do not explicitly disclose the use of proline specific endoprotease (PEP) that is **pepsin resistant** (i.e. active in the stomach of a patient), that has the hydrolytic activity at **pH below 5.5, or a pH optimum of below 6.5,** and that is obtained from an ***Aspergillus niger* sp.**, as required by the instant claims.

Dekker et al (2002) disclose such an enzyme (a prolyl endoprotease that can hydrolyze proline-rich peptides that are associated with celiac disease at a pH of below 5.5, or that has a pH optimum below 6.5; i.e. mimicking stomach pH, and that has been derived from *Aspergillus* sp., specifically *Aspergillus niger*) that can be used for digesting or hydrolyzing various types of proteins and peptides to obtain hydrolysates that can be used in various applications, including allergen free diets for babies, and for obtaining wheat gluten hydrolysates which are normally difficult to obtain (see Dekker et al, pages 3, 8 and 11, in particular; and claims) as they are poorly soluble at acidic pH (see page 3, last paragraph, in particular). They disclose the extensive usefulness and application of this PEP enzyme that acts well in acidic conditions with a pH optimum below 6.5 (preferably pH 3.5 to 6.5), and that can be used to digest wheat gluten from barley into digestible peptides in order to protect gastric mucosa, which is normally at acidic pH. Thus, Dekker et al explicitly disclose a suitable proline-specific endoprotease derived from

Aspergillus niger that is fully active in acidic pH environment (such as a mammalian stomach), and is not inactivated at low pH ranges such as below 6.5 (see page 12, last paragraph, in particular).

In brief, Dekker et al disclose a PEP enzyme isolated from *Aspergillus niger* that has acidic pH optimum (i.e. resistant to low pH environment such as mammalian stomach), and that effectively degrades proline-rich peptides that are allergenic and are associated with celiac sprue/disease.

Thus, given the disclosure from Dekker et al for a suitable prolyl endoprotease (derived from *Aspergillus niger* sp.) that can work best under the acidic pH conditions (such as of stomach of patients), an artisan of ordinary skill in the clinical art would have been motivated to substitute a better PEP enzyme (albeit obtained from an *Aspergillus* sp. such as *Aspergillus niger*), as explicitly taught by the referenced invention of Dekker et al in order to achieve a superior method of treatment (using an improved enzyme, that has an acidic pH optimum, similar to the stomach environment) of patients suffering from celiac disease. An artisan in the clinical art would have had a reasonable expectation of success in modifying the treatment method disclosed by Messer et al and Hausch et al, as evidenced by the disclosure of Dekker et al who demonstrate efficient *in vitro* digestion of various types of proline rich proteins using said prolyl endoprotease, (that has an acidic pH optimum, and therefore can remain active in acidic environment of mammalian stomach), and which will be suitable for the oral enzyme therapy as already suggested by the combined disclosure of Messer et al and Hausch et al (i.e. as an oral dietary supplement for hydrolyzing potentially harmful peptides in the stomach, before they reach the intestine of sensitive patients, the site of inflammatory reaction).

It is also noted that appellants have used the same PEP enzyme from *Aspergillus niger* sp. as specifically disclosed by Dekker et al that has all the inherent functional characteristics such as acidic pH optimum, pepsin resistance, etc. (see instant disclosure, page 12, line 21 through page 15, line 10) as currently recited in the amended claims of record. Therefore, the invention as claimed fails to distinguish itself over the combined teachings and/or suggestion from the cited prior art of record.

Thus, the invention as a whole would have been *prima facie* obvious to a person of ordinary skill in the art, at the time the claimed invention was made.

As per MPEP 2144.06, *In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on appellant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. In re Ruff, 256 F.2d 590, 118 USPQ 340 (CCPA 1958).*

As per MPEP 2111.01, *during examination, the claims must be interpreted as broadly as their terms reasonably allow. In re American Academy of Science Tech Center, F.3d, 2004 WL 1067528 (Fed. Cir. May 13, 2004)(The USPTO uses a different standard for construing claims than that used by district courts; during examination the USPTO must give claims their broadest reasonable interpretation.). This means that the words of the claim must be given their plain meaning unless appellant has provided a clear definition in the specification. In re Zletz*, 893 F.2d 319, 321, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989).

(10) Response to Argument

First, it is noted that appellants have made references to two NPL documents (Stepniak et al and Mitea et al; see brief, pages 11-12) as evidentiary support documents submitted earlier in the prosecution. However, as stated earlier in the final office action of record, these references have not been submitted as proper IDS (or PTO 1449) on the record, and therefore, have been considered by the examiner only to the extent as they pertain to appellant's current arguments, which are responded to hereinafter.

In response to appellant's arguments against the cited prior art references individually (see instant brief, pages 9-11), one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The argument that both Messer et al and Hausch et al "*teach away*" from the instant invention as they suggest use of "*enteric coating*", or use of PEP for breakdown of gliadin peptides "*in the BBM or in the intestine*" is not found to be persuasive because the combined disclosure of Messer et al and Hausch et al clearly provides the basis that the goal in the prior art is to "predigest" the gluten peptides (or antigenic or inflammatory peptides) before they reach patient's intestinal mucosa (where they cause inflammatory response, and therefore symptoms of celiac disease, etc.), and given the disclosure of Dekker et al for the appropriate PEP enzyme (that has low pH optimum, and that can work in acidic pH environments, such as mammalian stomach) from *Aspergillus niger*, an artisan of ordinary skill in the clinical art would have been motivated to substitute a better PEP enzyme that can work at acidic pH (i.e. not requiring an enteric coating for use in oral supplementation, and that can also be used *in vitro* to pre-digest hard to digest peptides in food products, as demonstrated by Dekker et al; see discussion above) of stomach as an enzyme therapy composition as specifically suggested by Hausch et al.

The limitations of the PEP being "*active in stomach*", or "*pepsin resistant*" are inherent in the PEP enzyme of Dekker (i.e. intrinsic functional properties/characteristics such as pH optimum, activity, selectivity/specificity, etc.) used to pre-digest the food proteins/products, or being used in the pharmaceutical composition that is being orally administered (i.e. ingested by

patient) to the subject in need thereof. Moreover, the suggestions of enteric coating are given in the prior art in order to protect the oral enzyme formulations that are not resistant to acidic pH environments (such as papain and bacterial prolyl endopeptidase used by Messer et al and Hausch et al, respectively) such as stomach. Since, Dekker et al disclose and demonstrate the fact that a specific PEP from *Aspergillus niger* has the capability to digest "allergenic peptides" contained in food products under acidic pH conditions (akin to mammalian stomach), a person of ordinary skill in the clinical art, at the time this invention was made, would have had a reasonable expectation of success in substituting and using Dekker's protease in place of the proline endoproteases used in the art (such as those in Messer et al and Hausch et al) that specifically need "enteric coating" and/or such protection.

Appellants' arguments regarding the disclosure of Hausch et al (WO 03/068170; see brief, page 10, last paragraph), which has not relied upon by the examiner in the prior art rejection of record, is noted. However, the argument that the "*.. intention of this coating is to deliver the enzyme to the intestine*" is also not found to be persuasive for the same reasons of record as discussed above.

The argument that "*.. Dekker describes the use of proline specific endoprotease in vitro rather than in vivo. While reference is made to reducing allergenicity of food (Dekker, page 7 lines 28-32), the enzyme is incubated with the food proteins prior to consumption. It would appear that enzymes used in this way are killed off during food preparation rather than during food digestion. Dekker is irrelevant to the method as claimed*" (see brief, page 11), is duly noted and fully considered. However, it is not found to be persuasive because, as noted earlier in the rejection, it is the same enzyme from Dekker et al, which is being used by appellants for the

instant invention as claimed and/or disclosed (see instant disclosure, page 12, line 21 through page 15, line 10), and therefore, the argument that "*Dekker is irrelevant to the method as claimed*", is interesting, but not found to be persuasive. Also, since, Dekker et al have demonstrated the *in vitro* pre-digestion of food products, in order to achieve allergen-free food products that are suitable for ingestion by sensitive subject populations that are affected by gluten peptides, it would stand an obvious reason why one of ordinary skill in the clinical art would be motivated to use and/or substitute such a superior PEP enzyme obtained from *A. niger*, as per their disclosure and/or suggestions for the treatment of celiac disease in a patient in need thereof. The argument that the "*enzymes used in this way are killed off during food preparation rather than during food digestion*" is also not found to be persuasive because an artisan of ordinary skill in the clinical art, at the time the claimed invention was made, would have fully contemplated the use of oral enzyme supplementation therapy for celiac sprue patients, wherein a better, stable PEP enzyme that is active in low pH environment of stomach, was substituted in a suitable pharmaceutical composition in order to eliminate the requirement of enteric coating, as well as to affect the pre-digestion of allergenic peptides, before they actually reach intestinal tissue of the susceptible patient, which is known in the prior art to be the primary site of inflammation in celiac disease.

Appellant's arguments of "*unexpected benefits*" based on the scientific publications of Stepniak et al and Mitea et al (submitted by appellants as evidence; see brief, pages 11-12) that demonstrate "*efficient gluten degradation*" using the *A. niger* PEP (Stepniak et al), or demonstrate efficient digestion of toxic gluten epitopes using said PEP in a "*validated dynamic system closely matching the human gastrointestinal tract (TIM system)"* is duly noted and fully

considered. However, such benefits arising out of the use and/or substitution of a superior enzyme (such as the PEP obtained from *A. niger* having an acidic pH optimum that can work in acidic pH environment such as a mammalian stomach, as explicitly disclosed by Dekker et al) in the enzyme therapy and/or supplementation *via* an oral pharmaceutical composition (i.e. for ingestion by a patient population in specific need thereof), would have been obvious and fully expected by an artisan of ordinary skill in the clinical art at the time of this invention, given the combined disclosure of the cited prior art references of record for use of such PEP enzyme for efficiently degrading proline-rich, allergenic food products containing toxic peptides. Thus the invention as claimed fails to distinguish itself over the combined teachings and/or suggestions of the cited prior art of record.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/Satyendra K. Singh/

Examiner, Art Unit 1653

Conferees:

/JON P WEBER/

Supervisory Patent Examiner, Art Unit 1657

/SUE LIU/

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